REMARKS:

In response to the restriction requirement dated January 25, 2007, applicants hereby elect the following species with traverse to start the prior art search.

Disease type: cardiac

Fibrosis cause: pressure stress in arterial hypertension

Proteasome inhibitor: threonine protease inhibitor MG132

Regarding the treatment agent, applicants contend that the treatment agents listed in the office action are not used in the presently claimed method but are recited in the present application as part of the description of the fibrosis model. In view of this, applicants do not believe that election of a treatment agent should be required since they are not actually administered in the presently claimed method.

The election is traversed on the grounds that Gyorkos does not teach the use of protease inhibitors for the treatment of fibrotic diseases. Gyorkos describes the use of a particular class of compounds as inhibitors of a serine protease, wherein the compounds are proposed for the treatment of cystic fibrosis, and other fibrotic diseases. Proteasome inhibitors as in the present invention are not inhibitors of a serine protease. Rather, proteasome inhibitors are compounds that interact with the catalytically active threonine of the proteolytic subunit of the proteasome, and thus inhibit the proteolytic activity of the 20S proteasome. Thus, the use of inhibitors of a serine protease for the therapy of fibrotic diseases does not suggest or disclose the presently claimed invention, since this compound class is different from the proteasome inhibitors used in the present invention.

The following is an extract from a review regarding the catalytic mechanism of the proteasome and the function of specific inhibitors of the proteasome (from Kisselev and Goldberg, Chem Biol 8: 739-758, 20011:

Regarding proteolytic activities of the 20S proteasome core particle:

Proteasomes form a new class of proteolytic enzymes called threonine proteases. Unlike any other protease, all the proteolytic sites in proteasomes utilize N-terminal threonines of β subunits as the active site nucleophiles. 20S core particles contain six active sites, three on each of its two central β-rings. These proteolytic sites differ in their specificities. Two termed "chymotrypsin-like" cut preferably after hydrophobic residues and have their catalytic residues located on the β5 subunits. Two sites, located on β2 subunits, are "trypsin-like" in cleaving after basic amino acids. The two remaining sites, located on β1 subunits, split peptide bonds preferentially after acidic residues. These latter sites are called "postacidic" or "caspase-like".

Regarding inhibitors of the 20S proteasome:

One can distinguish two distinct modes of proteasome inhibition: inhibition by direct modification of the catalytically active β-subunits and competitive binding to substrate binding sites or non-competitive inhibition by binding to the α-subunits and interference with substrate entry. The direct modification of the N-terminal Thr residues of the active sites is a common theme for several different classes of inhibitors. Specificity and reversibility of this reaction depends strongly on the pharmacophore group of the inhibitor: aldehydes are generally very reactive and form an instable hemiacetal bond with the hydroxylgroup of the Thr.

Peptide boronates are more potent and selective inhibitors than peptide aldehydes. Binding is practically irreversible over hours due to a very slow on and off rate. Vinyl sulfones (NLVS), lactacystin, and epoxyketones (e.g. epoxomycin) form stable and irreversible bonds with the active site Thr. An unusual group of inhibitors are the TMC-95s from Apiospora montagnei. These inhibitors bind the active sites noncovalently and are stabilized by forming a tight network of hydrogen bonds with several residues of the substrate pocket.

In view of the fact that the present invention makes a contribution over the cited prior art, applicants request that this restriction be reconsidered and withdrawn.

In the event that this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

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